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Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort

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ABSTRACT

Background: Personal care products (PCPs), a source of endocrine-disrupting chemical exposure, may be associated with the risk of hormone-sensitive cancers. Few studies have investigated associations for PCP use with the incidence of hormone-sensitive cancers or considered the joint effect of multiple correlated PCPs. We examined associations between frequently used, or "everyday", PCPs and incident cancers of the breast, ovary, and uterus with a fucus on the joint effect of multiple product exposure.

Methods: Sister Study participants (n=49 899) self-reported frequency of use in the year before enrollment (2003–2009) for 41 PCPs. Using five-level frequency categories based on questionnaire options, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the associations between multiple PCP use and incident breast, ovarian, and uterine cancer using quantile-based g-computation with Cox proportional hazards regression as the underlying model. Multiple PCP use was examined using groupings (beauty, hygiene, and skincare products) determined by both *a priori* knowledge and Spearman correlation coefficients for co-occurring product use. Associations between individual PCPs and the three cancers were also examined using Cox proportional hazards models coupling with Benjamini-Hochberg procedure for multiple comparisons.

Results: Over an average of 11.6 years, 4 226 breast, 277 ovarian, and 403 uterine cancer cases were identified. Positive associations were observed between the hygiene mixture and ovarian cancer (HR=1.35, 95%CI=1.00, 1.83) and the beauty mixture with postmenopausal breast cancer (HR=1.08, 95%CI=1.01, 1.16). Additionally, we observed an inverse association between the skincare mixture and breast cancer (HR=0.91, 95%CI=0.83, 0.99). No significant associations were observed for individual products after corrected for multiple comparison.

Conclusions: Findings from this multi-product, joint-effect approach contribute to the growing body of evidence for associations between PCPs and breast cancer and provides novel information on ovarian and uterine cancer.

1. Introduction

Breast, ovarian, and uterine cancer are considered hormone-driven cancers, with estrogen in particular thought to play a role in tumor development and growth. These cancers continue to be major health threats for women with an incidence slightly increasing worldwide (Yi et al., 2021). In 2022, cancers of the breast, ovary, and uterus were estimated to contribute to over 370 000 incident cases (>19% of all new cancer cases) and 68 610 deaths (>11% of all cancer deaths) in the U.S (Siegel et al., 2022).

Established risk factors for hormone-sensitive cancers, including obesity (Stephenson & Rose, 2003), early menarche (Collaborative Group on Hormonal Factors in Breast Cancer, 2012), parity (Lambe et al., 1996), and use of hormonal contraceptives (Mørch et al., 2017) or hormone replacement therapy (Narod, 2011), provide evidence for endocrine disruption and/or hormonal imbalance as key biologic pathways. There has been a growing interest in the role of endocrine-disrupting chemicals (EDCs) in hormone-sensitive cancer etiology given the shared secular trends for EDC production, precocious puberty, and breast cancer incidence (Bergman et al., 2013; Calaf et al., 2020;

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Lucaccioni et al., 2020). Some previous epidemiologic studies have investigated the associations between EDCs and hormone-sensitive cancers (Ahern et al., 2019; Liu et al., 2021; López-Carrillo et al., 2010; Parada et al., 2019; Reeves et al., 2019; Sarink et al., 2021; Wu et al., 2021). However, conclusions from these studies were inconsistent and limited, likely due to the use of transient exposure biomarkers to estimate relevant exposure levels to assess long-term risk of carcinogenesis (Zuccarello et al., 2018). Experimental studies have demonstrated the ability of different EDCs such as bisphenol A (Shi et al., 2017; Wang et al., 2016), triclosan (Farasani & Darbre, 2021), parabens (Charles & Darbre, 2013), and phthalates (Moral et al., 2011), to affect hormone-sensitive tumor development and progression, sometimes even at low-dose exposures.

PCPs have been important sources of chronic exposure to short-lived EDCs such as bisphenols, parabens, phthalates, triclosan, and fragrances (Branch et al., 2015; Braun et al., 2014; Dodson et al., 2012; Helm et al., 2018; Myers et al., 2015; Peinado et al., 2021; Sakhi et al., 2017). Although women are the primary consumers of PCPs and have been disproportionally burdened by EDC exposures (Biesterbos et al., 2013; Silva et al., 2004), few epidemiologic studies have investigated the contribution of PCP use to the risk of women's hormone-sensitive cancers. Existing research has largely focused on only certain products such as hair dyes, hair straighteners/relaxers, deodorant, genital talc, and douching products (Allam, 2016; Brinton et al., 2018; Chang et al., 2022; Eberle et al., 2020; Gonzalez et al., 2016; Goodman et al., 2020; Mousavi & Vaghar, 2021; O'Brien et al., 2019, 2021; Penninkilampi & Eslick, 2018; Rylander et al., 2019; Stiel et al., 2016; Taylor et al., 2018; Wentzensen & O'Brien, 2021; White et al., 2021), without considering a comprehensive list of more frequently used ("everyday") PCPs. Furthermore, due to the challenges of data collection on a wide range of PCPs and statistical methods for mixture analyses, previous studies predominately assessed the effect of individual products separately. Taking a single-product approach is limiting because it fails to account for potential confounding by concurrently used products and does not reflect the risk associated with multiple products simultaneously in real-life settings (Braun et al., 2014).

In this study, we aimed to examine the associations between the use of everyday PCPs and cancers of the breast, ovary, and uterus with a focus on joint effect of multiple product use in a large prospective cohort in the U.S. We also explored whether these relationships varied by race and ethnicity, and body mass index (BMI). Racial and ethnic differences in PCP use were observed previously (Collins et al., 2021; Dodson et al., 2021; Gaston et al., 2020; Preston et al., 2021; Wu et al., 2010), andthe products marketed toward or used often by women of color may contain more harmful and hormonally-active chemicals (Helm et al., 2018), which may contribute to a differential impact of PCP use on cancer development by race and ethnicity. We also hypothesized that the effect of PCP use may differ by BMI, as exogenous estrogens such as hormone replacement therapy have a reduced impact on breast and endometrial cancer in obese than lean women ("Endometrial Cancer and Hormone-Replacement Therapy in the Million Women Study," 2005; Hou et al., 2013).

2. Methods

2.1. Study design and population

The Sister Study is a prospective cohort that enrolled 50 884 women who lived in the United States, including Puerto Rico, from 2003 to 2009 (Sandler et al., 2017). Participants were eligible if they were between 35 and 74 years old at enrollment and had at least one sister diagnosed with breast cancer, but themselves were breast cancer-free. At baseline, participants completed a computer-assisted telephone interview and self-administered written questionnaires to assess demographics characteristics, lifestyle factors, and reproductive history. Weight and height were measured by trained examiners during a home visit at baseline. Participants are contacted annually for health updates regarding new cancer diagnoses and other health-related changes. More detailed follow-up assessments are collected every three years. Response rates have been above 80% throughout follow-up. Data for the current analysis included person-time through October 2020 (Data Release 10.1). Written informed consent was obtained from all participants, and the Sister Study is overseen by the institutional review boards of the National Institutes of Health.

Among 49 889 women who responded to at least one PCP question, we excluded women who withdrew from the study, had a pre-baseline diagnosis, an uncertain diagnosis, or an unclear timing of diagnosis (relative to enrollment) for the hormone-sensitive cancer of interest, or who did not contribute any follow-up time. For ovarian and uterine cancer analysis, we further excluded women who had a pre-baseline bilateral oophorectomy or hysterectomy, respectively. Thus, the numbers of eligible participants varied by analyses, with 49 578, 40 610, and 33 976 participants included in the breast, ovarian, and uterine cancer analyses, respectively.

2.2. Assessment for personal care product use

Participants completed a questionnaire at baseline about their use of PCPs in the previous 12 months. The questions collected information on the frequency of use of 41 PCPs, including 12 beauty products (blush/rouge, eyeliner, eye shadow, foundation, lipstick, mascara, perfume/cologne, makeup remover, artificial nails/fill-ins, cuticle cream, nail polish, and nail polish remover), seven everyday hair products (conditioner, hair food, hair spray, hair styling gel/mousse, Minoxidil/Rogaine, pomade/hair grease, shampoo), eight hygiene products (bath/shower gel, deodorant/antiperspirant, douche, mouthwash/rinse, shaving cream, talc [under arm], talc [genital], talc [other areas]), and 14 skincare products (anti-aging or wrinkle product, age spot lightener, baby oil/mineral-based oil, blemish/acne product, body lotion/cream, cleansing cream, face cream/moisturizer, facial mask, foot cream/moisturizer, hand lotion/cream, lip moisturizer, petroleum jelly, skin lightener, self-tanner) with the options of "did not use", "less than once a month", 1–3 times per month", "1–5 times per week", and "more than 5 times per week." We classified those options from low to high frequency of use as level one to five. Seven less frequently used hair products including permanent, semi-permanent, and temporary dyes, bleach, highlights, straighteners/relaxers or pressing products, and hair permanents/body waves were not considered, as use of these products is more episodic and thus would not regularly co-occur with the everyday PCPs.

2.3. Incident hormone-sensitive cancers

Participants who reported a diagnosis of breast, ovarian (including fallopian tube and peritoneal cancers), and/or uterine cancer were defined as cases. We further asked the women who reported a hormone-sensitive cancer diagnosis for permission to retrieve their medical records. About 89%, 78%, and 78% of the cases were confirmed with either medical records or death certificates indicating the primary or underlying cause of death as breast, ovarian, and uterine cancer, respectively. The positive predictive values of self-reported cases in relation to medically confirmed cases are high, with 99% for breast, 80% for ovarian, and 81% for uterine cancer (The Sister Study: Breast Cancer Validation, 2022); thus, all self-reported cases were included in the main analyses.

We also abstracted information on cancer subtypes such as estrogen receptor (ER) status of breast cancer, invasiveness of breast cancer (invasive or ductal carcinoma in situ [DCIS]), ovarian cancer type (serous or non-serous) (Peres et al., 2019), and uterine cancer type (endometrial; type I or type II endometrial) (Clarke et al., 2019).

2.4. Covariates

All the included covariates were assessed at baseline. These include self-reported demographic characteristics (age, race and ethnicity, educational attainment, and household income), reproductive history (age at menarche, age at first birth, breastfeeding duration, menopausal status, parity, oral contraceptive use, and hormone replacement therapy use), and relevant lifestyle factors such as smoking status and alcohol consumption. Information on recreational physical activity in the past 12 months including type, frequency, and duration was used to calculate metabolic equivalent (MET)-hours (Ainsworth et al., 2000). We collected self-reported urbanicity and evaluated neighborhood deprivation using Area Deprivation Index (Singh, 2003) for the participant's residential address. BMI was calculated using examiner measured height and weight. Detailed information on data collection and questionnaires can be found on the Sister Study website (The Sister Study: For Researchers, 2022).

2.5. Statistical analysis

Descriptive analyses of covariates including means and standard deviations were presented by breast, ovarian, and uterine cancer outcomes. Pairwise correlations were estimated for frequency of PCP use within and across four *a priori* identified product groups (i.e., beauty, hair, hygiene, and skincare), and between PCP use and covariates using Spearman's rank correlation coefficients.

The joint effects (φ) of PCP use on hormone-sensitive cancers were estimated using quantile-based g-computation with the underlying models as Cox proportional hazards regressions and age as the timescale. Participants were considered at-risk from age at enrollment until the earliest age of occurrence of the hormone-sensitive cancer diagnosis, gynecological surgery relevant to the specific outcome being analyzed (i.e., oophorectomy for ovarian cancer analysis and hysterectomy for uterine cancer analysis), last follow-up, or death. To evaluate the contribution of individual products in each of the mixtures, independent effect sizes (β) and weights (w) of d products estimated from the underlying Cox models were presented. Briefly, β_j is given as the independent effect size of product j (where $\sum_{j=1}^{d}\beta_j$ equals to φ) and w_k is given as a weight for product k among d products with the same directionality (where $w_k = \beta_k / \sum_j^d \beta_j$) (Keil et al., 2020). We estimated joint effects of products in each group that were positively but not negatively correlated, where joint effects may be of little relevance to use patterns. Cox proportional hazards regressions were also used to estimate the associations between use of single products and hormone-sensitive cancers.

The five-level frequency categories of PCP use were treated as continuous variables in all of our analyses, assuming an approximate linear relationship and uniform change in the hazard for each increase in the frequency measure. More specifically, the ordinal values based on usage frequency instead of quantiles was used in quantile-based g-computation. We further examined potential non-linearity by conducting a Wald test for a quadratic term of frequency of PCP use. The proportional hazards assumption of Cox models was evaluated by assessing correlations between the scaled Schoenfeld residuals and time using goodness-of-fit tests combined with visual inspections of the residual plots. A global test of fit was performed to assess the proportional hazards assumption for quantile-based g-computation models.

We determined potential confounders based on the previous literature and evaluating relationships between the covariates, PCP use, and outcomes from bivariate analyses. All models were adjusted for race and ethnicity (Black or African American including Black Hispanic/Latina, Hispanic/Latina non-Black, non-Hispanic White/Latina, and all others, including Asian/Pacific Islander or American Indian; as a proxy for unmeasured social constructs), educational attainment (high school or less, some college, college and above), annual household income (<$50,000, $50,000-<$100,000, ≥$100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (MET-hours per week, continuous, linear), BMI (kg/m^2, continuous, restricted cubic spline), and a product term between BMI and menopausal status at enrollment to account for opposing roles of BMI in hormone-sensitive cancer development before and after menopause (Carmichael & Bates, 2004; Qureshi et al., 2020). We used the Benjamini-Hochberg procedure to correct for multiple comparisons only for the analyses estimating the effects of single products (Benjamini & Hochberg, 1995).

We evaluated the joint effect of PCP use and hormone-sensitive cancers by menopausal status and cancer subtypes. For analyses by menopausal status, participants who transitioned from pre- to postmenopause during follow-up were censored for premenopausal cancer at age of menopause, at which time they were considered at-risk for postmenopausal cancer. Person-time after age at menopause was considered postmenopausal cancer risk time. *P*-values for heterogeneity (*p*-for-heterogeneity) by menopausal status and cancer subtypes were estimated using Wald tests of outcome-by-product interaction terms from joint adjusted models (Xue et al., 2013). Stratum-specific hazard ratios (HRs) for race and ethnicity and BMI were estimated by augmenting our primary model with modifier-by-product interaction terms, and heterogeneity was tested using Wald tests on the interaction terms. Race-specific HRs were only calculated for Black and non-Hispanic White but not for other racial and ethnic groups due to limited sample sizes.

For sensitivity analysis, we first restricted the outcomes to only medically confirmed cases. We then evaluated whether age at menarche, age at first birth, parity, breastfeeding duration, Area Deprivation Index, and urbanicity confounded the associations between PCP use and hormone-sensitive cancers by additional adjustment. We considered the significant level an alpha <0.05 to determine statistical significance for the mixture models, and a Benjamini-Hochberg multiple comparison corrected *p*-value <0.05 for the single-product models. Complete case analysis was done given the low percentage (3–5%) of missing data agglomerated over all analytic variables for each model. All analyses were conducted in R version 4.2.1.

3. Results

After an average of 11.6 years of follow-up, 4 226 breast cancer, 277 ovarian cancer, and 403 uterine cancer cases were identified in the this study. Participant characteristics by whether they were included or excluded for each cancer analyses are detailed in Table 1 & S1. Among 49 578 participants in the breast cancer analyses, 8% self-reported as Black, over 84% as non-Hispanic White, and less than 8% as Hispanic and other races and ethnicities. Approximately one-third of the participants had annual household income of more than $100 000 and more than half had at least a college education.

The correlation coefficient matrix between frequency categories of PCP use is presented in Fig. 1 and Table S2. We observed positive correlation coefficients between products within beauty, hygiene, and skincare product mixtures with beauty products showing generally higher correlations. Spearman correlation coefficients (r_s) ranged from 0.23 to 0.57 for eyeliner, eyeshadow, foundation, lipstick, mascara, and makeup remover; r_s was 0.91 between nail polish and nail polish remover. Higher correlations were also observed between different types of talc use (r_s=0.34–0.50). Due to the weaker and in some cases inverse correlation coefficients between frequency of hair products use, we did not estimate the joint effect of hair products with hormone-sensitive cancers (i.e, we did not consider hair products as a mixture that people use together).

Fig. 2 and Table S3 show the Spearman correlation coefficients

Table 1
Descriptive statistics of breast, ovarian, and uterine cancer cases and non-cases in the Sister Study (enrolled 2003–2009).

	Eligible cohort for breast cancer analysis (n=49578)[a]		Eligible cohort for ovarian cancer analysis (n=40610)[b]		Eligible cohort for uterine cancer analysis (n=33976)[c]	
Characteristics	Case (n=4226)	Non-case (n=45352)	Case (n=277)	Non-case (n=40333)	Case (n=403)	Non-case (n=33573)
Age at baseline (year); mean (SD)	57.0 (8.80)	55.6 (8.97)	57.6 (8.66)	54.9 (8.99)	57.7 (8.16)	54.2 (8.94)
Follow-up time (year); mean (SD)	6.44 (3.85)	12.1 (2.70)	6.36 (3.73)	11.7 (3.18)	6.82 (3.83)	11.6 (3.34)
Race and ethnicity; n (%)						
Black	338 (8.0%)	3924 (8.7%)	24 (8.7%)	3402 (8.4%)	33 (8.2%)	2498 (7.4%)
Hispanic non-Black	144 (3.4%)	2076 (4.6%)	8 (2.9%)	1842 (4.6%)	16 (4.0%)	1498 (4.5%)
Non-Hispanic White	3635 (86.0%)	38159 (84.1%)	240 (86.6%)	34046 (84.4%)	347 (86.1%)	28727 (85.6%)
Other[d]	108 (2.6%)	1189 (2.6%)	5 (1.8%)	1039 (2.6%)	7 (1.7%)	847 (2.5%)
Annual household income; n (%)						
<$50,000	1068 (25.3%)	11613 (25.6%)	80 (28.9%)	9774 (24.2%)	116 (28.8%)	7515 (22.4%)
$50,000-$100,000	1709 (40.4%)	18598 (41.0%)	116 (41.9%)	16478 (40.9%)	166 (41.2%)	13728 (40.9%)
≥$100,000	1449 (34.3%)	15141 (33.4%)	81 (29.2%)	14081 (34.9%)	121 (30.0%)	12330 (36.7%)
Educational attainment; n (%)						
High school or less	617 (14.6%)	6988 (15.4%)	53 (19.1%)	5826 (14.4%)	49 (12.2%)	4479 (13.3%)
Some college	1335 (31.6%)	15352 (33.9%)	95 (34.3%)	13117 (32.5%)	126 (31.3%)	10365 (30.9%)
College or above	2273 (53.8%)	23004 (50.7%)	129 (46.6%)	21383 (53.0%)	228 (56.6%)	18723 (55.8%)
Area Deprivation Index (percentile); mean (SD)	33.1 (24.3)	34.3 (24.5)	33.3 (24.3)	33.5 (22.6)	32.7 (23.6)	32.1 (24.1)
Urbanicity						
Urban	819 (19.4%)	8729 (19.2%)	43 (15.5%)	7807 (19.4%)	86 (21.3%)	6462 (19.2%)
Suburban, small town, other	2600 (61.5%)	27099 (59.8%)	180 (65.0%)	24454 (60.6%)	242 (60.0%)	20652 (61.5%)
Rural	804 (19.0%)	9427 (20.8%)	52 (18.8%)	7991 (19.8%)	75 (18.6%)	6400 (19.1%)
Alcohol consumption; n (%)						
Never or past	802 (19.0%)	8575 (18.9%)	65 (23.5%)	7153 (17.7%)	74 (18.4%)	5523 (16.5%)
Current < 1 drink/day	2811 (66.6%)	30590 (67.5%)	182 (65.7%)	27490 (68.2%)	277 (68.7%)	23123 (68.9%)
Current ≥ 1 drinks/day	609 (14.4%)	6108 (13.5%)	30 (10.8%)	5624 (13.9%)	52 (12.9%)	4870 (14.5%)
Smoking status; n (%)						
Never	2287 (54.1%)	25556 (56.4%)	143 (51.6%)	22879 (56.7%)	214 (53.1%)	19172 (57.1%)
Past or current	1939 (45.9%)	19783 (43.6%)	134 (48.4%)	17444 (43.3%)	189 (46.9%)	14392 (42.9%)
Parity; n (%)						
0–1	1408 (33.3%)	14708 (32.4%)	101 (36.5%)	13263 (32.9%)	146 (36.2%)	11665 (34.7%)
2	1554 (36.8%)	16685 (36.8%)	92 (33.2%)	14908 (37.0%)	152 (37.7%)	12332 (36.7%)
3	1264 (29.9%)	13927 (30.7%)	83 (30.0%)	12137 (30.1%)	104 (25.8%)	9554 (28.5%)
Age at first birth (year); n (%)						
Nulliparous	776 (18.4%)	8195 (18.1%)	60 (21.7%)	7456 (18.5%)	90 (22.3%)	6683 (19.9%)
<23	1293 (30.6%)	14518 (32.0%)	101 (36.5%)	11878 (29.4%)	118 (29.3%)	8496 (25.3%)
23–27	1016 (24.0%)	10595 (23.4%)	59 (21.3%)	9346 (23.2%)	108 (26.8%)	7668 (22.8%)
≥27	1141 (27.0%)	11998 (26.5%)	56 (20.2%)	11618 (28.8%)	86 (21.3%)	10696 (31.9%)
Menopausal status at baseline; n (%)						
Premenopausal	1270 (30.1%)	15186 (33.5%)	90 (32.5%)	16376 (40.6%)	114 (28.3%)	14025 (41.8%)
Postmenopausal	2956 (69.9%)	30152 (66.5%)	187 (67.5%)	23946 (59.4%)	289 (71.7%)	19538 (58.2%)
Oral contraceptive use; n (%)						
None	692 (16.4%)	7214 (15.9%)	48 (17.3%)	6245 (15.5%)	91 (22.6%)	5085 (15.1%)
<2 years	632 (15.0%)	7191 (15.9%)	60 (21.7%)	6174 (15.3%)	81 (20.1%)	4932 (14.7%)
2-<10 years	1810 (42.8%)	19471 (42.9%)	119 (43.0%)	17286 (42.9%)	167 (41.4%)	14316 (42.6%)
≥10 years	1089 (25.8%)	11427 (25.2%)	50 (18.1%)	10586 (26.2%)	63 (15.6%)	9210 (27.4%)
Hormone replacement therapy use[e]; n (%)						
None	2220 (52.5%)	25211 (55.6%)	135 (48.7%)	25630 (63.5%)	261 (64.8%)	22559 (67.2%)
Estrogen alone	814 (19.3%)	8874 (19.6%)	56 (20.2%)	4320 (10.7%)	36 (8.9%)	2296 (6.8%)
Estrogen plus Progestin	1184 (28.0%)	11135 (24.6%)	86 (31.0%)	10275 (25.5%)	104 (25.8%)	8637 (25.7%)
Age at menarche (year); n (%)						
<12	3290 (77.9%)	36130 (79.7%)	216 (78.0%)	32385 (80.3%)	302 (74.9%)	27278 (81.2%)
≥12	931 (22.0%)	9182 (20.2%)	61 (22.0%)	7915 (19.6%)	101 (25.1%)	6266 (18.7%)
Breast feeding duration (month); n (%)						
<48	3125 (73.9%)	33127 (73.0%)	223 (80.5%)	28851 (71.5%)	316 (78.4%)	23472 (69.9%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Eligible cohort for breast cancer analysis (n=49578)[a]		Eligible cohort for ovarian cancer analysis (n=40610)[b]		Eligible cohort for uterine cancer analysis (n=33976)[c]	
	Case (n=4226)	Non-case (n=45352)	Case (n=277)	Non-case (n=40333)	Case (n=403)	Non-case (n=33573)
≥48	1095 (25.9%)	12162 (26.8%)	53 (19.1%)	11429 (28.3%)	86 (21.3%)	10056 (30.0%)
Physical activity (metabolic equivalent MET-hours/week); mean (SD)	49.7 (31.0)	50.8 (31.4)	54.4 (37.5)	50.7 (31.2)	47.0 (32.4)	50.8 (31.3)
Body mass index (kg/m^2); mean (SD)	28.2 (6.29)	27.7 (6.24)	28.3 (6.22)	27.5 (6.18)	30.7 (7.41)	27.2 (6.11)

SD: standard deviation.

[a] Excluded women who withdrew (n=4), were diagnosed with breast cancer before baseline (n=59), had an uncertain breast cancer history (n=5), had an unclear timing of diagnosis relative to enrollment (n=17), did not contribute any follow-up time (n=287), did not respond all questions about personal care product (n=931). Missing: race and ethnicity (n=5), educational attainment (n=9), Area Deprivation Index (n=956), urbanicity (n=100), alcohol consumption (n=83), smoking status (n=13), parity (n=32), age at first birth (n=46), menopausal status (n=7), oral contraceptive use (n=52), hormone replacement therapy use (n=140), age at menarche (n=45), breast feeding duration (n=69), physical activity (n=417), body mass index (n=15).

[b] Excluded women who withdrew (n=4), were diagnosed with ovarian cancer before baseline (n=204), had an uncertain uterine cancer history (n=13), had an unclear timing of diagnosis relative to enrollment (n=30), had a bilateral oophorectomy prior to enrollment (n=8998), did not contribute any follow-up time (n=233), or did not respond all questions about personal care product use (n=792). Missing: race and ethnicity (n=4), educational attainment (n=7), Area Deprivation Index (n=749), urbanicity (n=83), alcohol consumption (n=66), smoking status (n=10), parity (n=26), age at first birth (n=36), menopausal status (n=4), oral contraceptive use (n=42), hormone replacement therapy use (n=108), age at menarche (n=33), breast feeding duration (n=54), physical activity (n=330), body mass index (n=11).

[c] Excluded women who withdrew (n=4), were diagnosed with uterine cancer before baseline (n=381), had an uncertain uterine cancer history (n=12), had an unclear timing of diagnosis relative to enrollment (n=55), had a hysterectomy prior to enrollment (n=15599), did not contribute any follow-up time (n=183), or did not respond all questions about personal product use (n=674). Missing: race and ethnicity (n=3), educational attainment (n=6), Area Deprivation Index (n=595), urbanicity (n=59), alcohol consumption (n=57), smoking status (n=9), parity (n=23), age at first birth (n=31), menopausal status (n=4), oral contraceptive use (n=31), hormone replacement therapy use (n=83), age at menarche (n=29), breast feeding duration (n=46), physical activity (n=270), body mass index (n=11).

[d] Other including Asian/Pacific Islander (26–31%), American Indian (7%), other (61–68%), and unknown (0.5%).

[e] For the breast and ovarian cancer analyses, the women who ever reported using estrogen plus Progestin hormone replace therapy were categorized as estrogen plus Progestin. For uterine cancer analysis, the women who ever reported using estrogen alone hormone replace therapy were categorized as estrogen alone.

matrix between frequency of PCP use and characteristics of study participants. Overall, PCP use was correlated with age, race and ethnicity, income, menopausal status, and BMI. Women who were older and postmenopausal at enrollment used most PCPs less frequently, except for some products such as lipstick. Black women more frequently used hair food, pomade, douche, baby oil, and petroleum jelly, and non-Hispanic White women more frequently used blush, mascara, hair spray, hair styling products, and self-tanner than other races and ethnicities. Positive correlations were mostly observed between income and beauty, hair, and skincare products, and BMI and hygiene products.

Table 2 and Figs. 3-5 show the joint effects of a one-frequency increase in use of PCP mixtures on hormone-sensitive cancers. In the adjusted quantile-based g-computation, the beauty mixture was positively associated with breast cancer (HR=1.05, 95%CI=0.99, 1.12) with the top three drivers being artificial nails (weight=26.5%), nail polish remover (weight=15.1%) and mascara (weight=15.0%) (Table S4). Moreover, the beauty product mixture showed positive associations of similar magnitude with ovarian (HR=1.08, 95%CI=0.85, 1.37) and uterine cancer (HR=1.08, 95%CI=0.88, 1.34) to those observed for breast cancer; however, the confidence intervals were wider (Figs. 4 & 5). For the hygiene mixture, we observed a positive association with ovarian cancer incidence (HR=1.35, 95%CI=1.00, 1.83), with douche as the most important component (weight=57.6%) (Table S4). In contrast, an inverse association was found between the skincare mixture and breast cancer incidence (HR=0.91, 95%CI=0.83, 0.99) with self-tanner (weight=24.9%), baby oil (weight=20.9%), and age spot lightener (weight=18.1%) as the most important contributors (Fig. 5 & Table S4). We observed use of the beaty mixture positively associated with postmenopausal breast cancer (HR=1.08, 95%CI=1.01, 1.16) but not premenopausal breast cancer cases (HR=0.90, 95%CI=0.76, 1.07) with a *p*-for-heterogeneity=0.05 (Table 2).

Results for the adjusted single-product models are shown in Figs. 3-5 & Table S5. No associations were statistically significant after adjusting for multiple comparisons. However, some associations were observed for a one-frequency increase in use of some PCPs. For example, for breast cancer, inverse associations were observed for use of talc under arm (HR=0.96, 95%CI=0.92, 0.99) and baby oil (HR=0.96, 95%CI=0.93, 1.00); an elevated hazard was found for deodorant (HR=1.03, 95% CI=1.00, 1.07). We observed a stronger positive association between douche and ovarian cancer incidence (HR=1.31, 95%CI=1.06, 1.63). For uterine cancer, elevated hazards for cuticle cream (HR=1.15, 95% CI=1.03, 1.29) and petroleum jelly (HR=1.10, 95%CI=1.01, 1.20) were observed.

We observed an elevated association between the beauty mixture and breast cancer among non-Hispanic White women but not Black women (non-Hispanic White HR=1.08, 95%CI=1.01, 1.15; Black HR=0.85, 95%CI=0.68, 1.05; *p*-for-heterogeneity=0.04; Table 3). In contrast, the association of the beauty mixture with ovarian cancer was evident for Black women but not for non-Hispanic White women (Black HR=3.62, 95%CI=1.55, 8.46; non-Hispanic White HR=0.95, 95% CI=0.72, 1.24; *p*-for-heterogeneity<0.01). When stratifying the joint effects by BMI (Table 4), stronger positive associations for the hygiene and skincare mixtures with ovarian cancer were observed in women with a BMI <25 kg/m^2 compared to those with a BMI equal or above 25 kg/m^2 (*p*-for-heterogeneity≤0.01 [hygiene], 0.03 [skincare]).

We did not observe non-linear relationships or violation of Cox proportional hazard assumption. Comparable joint effects were observed when restricting breast cancer cases to ER+ or invasive disease, whereas wider confidence intervals were present for ER- and *in* situ cancers (Table S6). A borderline significance for heterogeneity (*p*-value=0.07) by ER status was found for the association between the beaty mixture and breast cancer (ER+ HR=1.04, 95%CI=0.97, 1.12; ER- HR=0.88, 95%CI=0.73, 1.04). We also observed similar effects of the PCP mixtures on serous and all ovarian cancers, and on endometrial cancer, type 1 endometrial cancer, and all uterine cancer cases. In sensitivity analyses, we did not observe a major departure when limiting

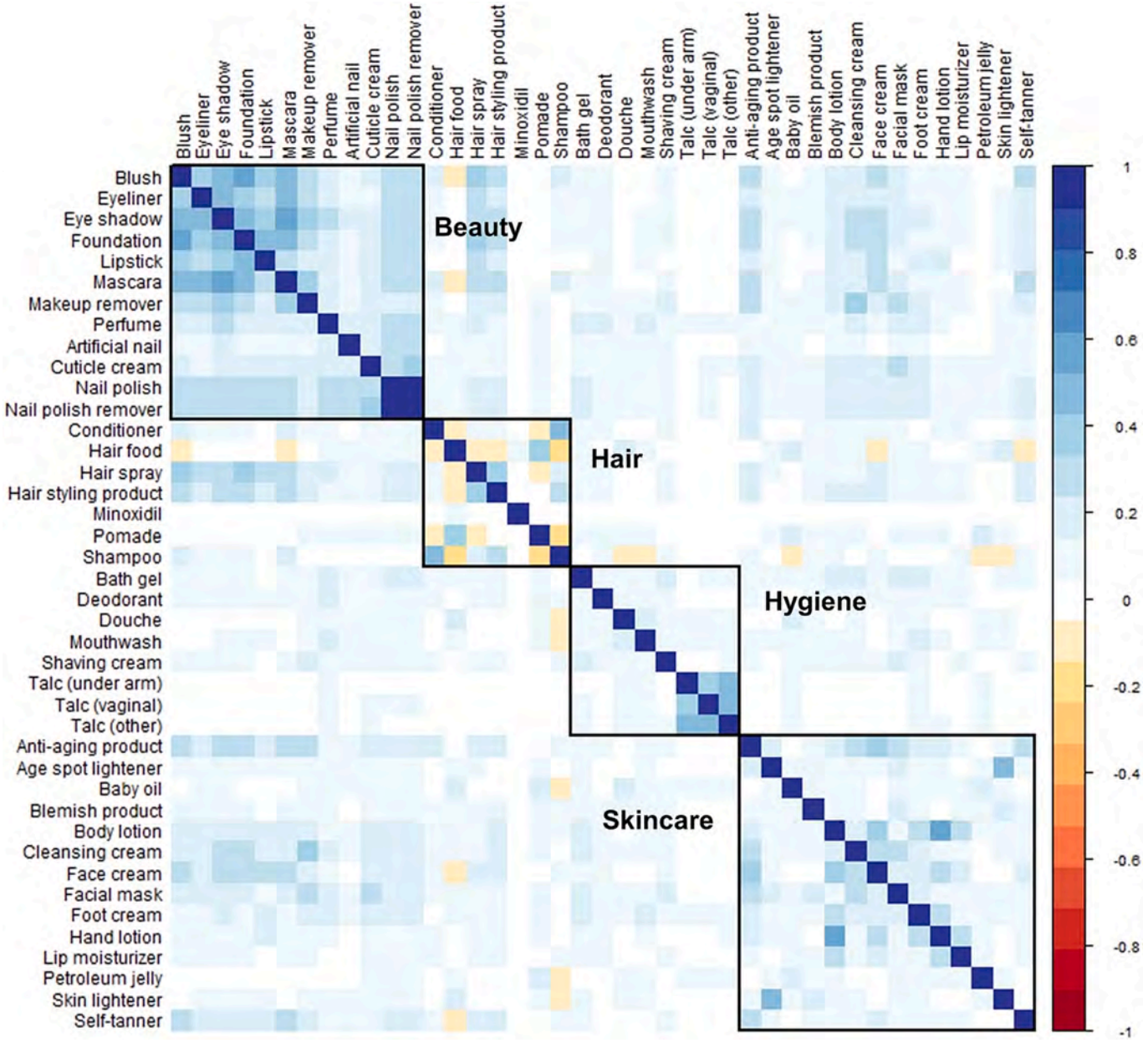

Fig. 1. Spearman correlation coefficient matrix for frequency of personal care product use.

to medically confirmed cases although associations between the beauty mixture and breast cancer and between the hygiene mixture and ovarian cancer were slightly attenuated (Table S7). When further adjusting for potential confounders such as other reproductive-related variables, Area Deprivation Index, and urbanicity, our results remain unchanged (Table S8).

4. Discussion

In this large U.S.-wide prospective cohort study, we observed joint effects of the hygiene mixture on ovarian cancer and the beauty mixture on postmenopausal breast cancer. We also found an inverse association between the skincare mixture and breast cancer. No statistically significant association between individual PCP and hormone-sensitive cancers was observed after correcting for multiple comparisons. To our knowledge, this is the first study to consider the joint effect of everyday PCP mixtures on hormone-sensitive cancers.

Taylor et al. (2018) estimated associations between PCP use and breast cancer incidence in the Sister Study (with follow-up through June 2014) using latent class analysis (LCA) combined with Cox proportional hazard models (Taylor et al., 2018). With an additional six years of follow-up and over 1 900 more breast cancer cases, our current results were mostly consistent with the previously reported findings, particularly the relationship between increased use of beauty products and a higher postmenopausal breast cancer incidence. Our results differ however with regards to the skincare mixture. Taylor et al., observed an elevated association whereas we observed an inverse association between the skincare mixture and breast cancer. This discrepancy can be partly explained by the different statistical approaches used in these two studies. While quantile-based g-computation estimates the joint effect of one-frequency level increase in all the PCPs included in the mixture, the approach combining LCA with Cox proportional hazard regression estimates the associations between the groups of women with different exposure profiles and incident breast cancer. Notably, some hygiene products positively contributing to breast cancer in the current analyses such as deodorant and shaving cream or some skincare products

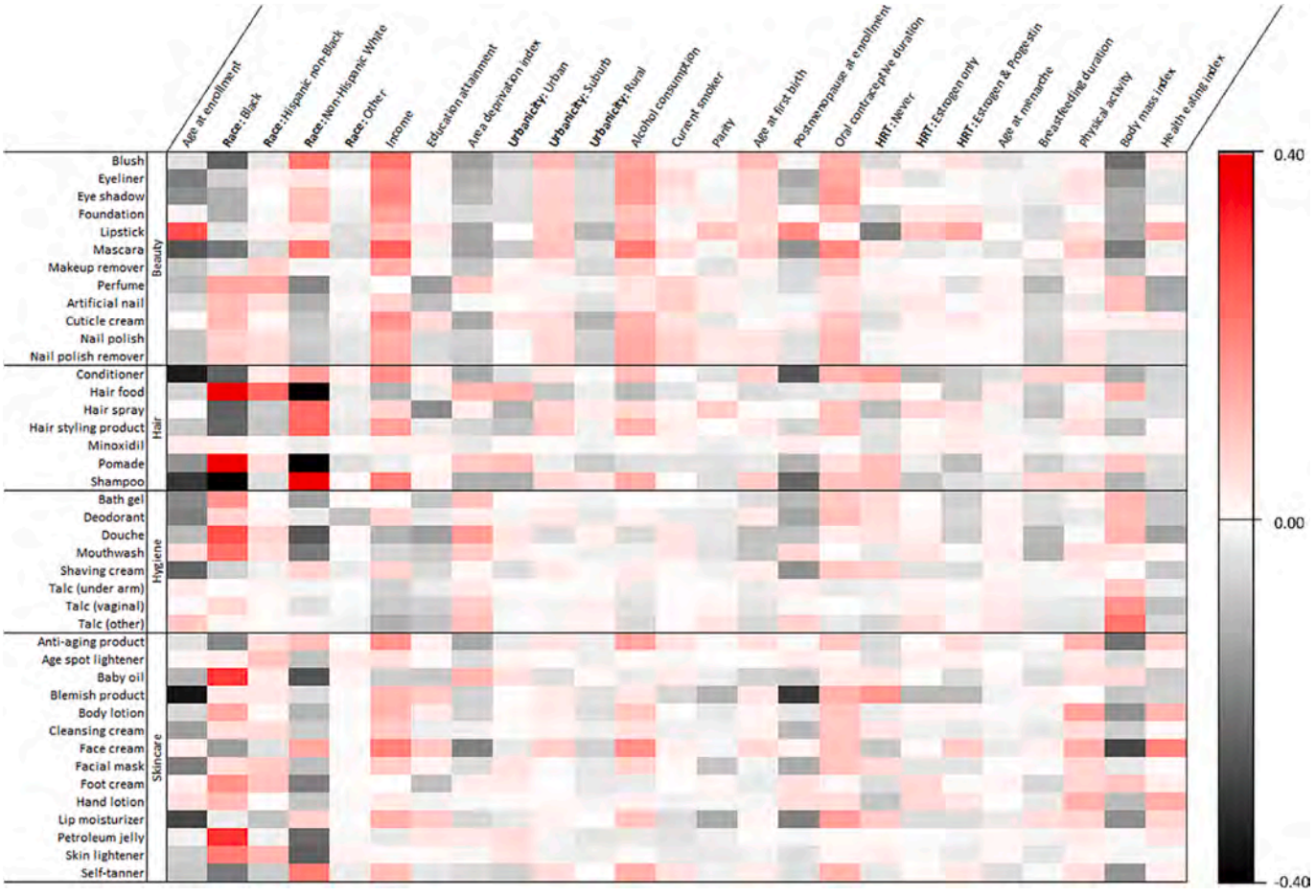

Fig. 2. Spearman correlation coefficients for frequency of personal care product use and covariates. [Note: Race and ethnicity, urbanicity, and HRT were coded as binary covariates for each category.]

inversely associated with breast cancer such as age spot lightener, baby oil, lip moisturizer, and self-tanner were not included in Taylor et al.'s LCA-based grouping due to a lack of variability in posterior probability of these products across the groups.

Results from previous studies investigating associations between everyday PCP use and hormone-sensitive cancers have focused on use of individual products, including associations for deodorant with breast cancer (Allam, 2016; Linhart et al., 2017; Mousavi & Vaghar, 2021) and talc and douche with ovarian (Gonzalez et al., 2016; Goodman et al., 2020; Penninkilampi & Eslick, 2018; Wentzensen & O'Brien, 2021) and uterine cancer (O'Brien et al., 2019, 2021). Similar to some previous studies (Allam, 2016; Mousavi & Vaghar, 2021), the elevated association between deodorant use and breast cancer was modest and not statistically significant in the single-product models, moreover, no evidence of a positive association between the hygiene mixture (containing deodorant) and breast cancer was observed. We observed a positive association for the hygiene mixture in relation to incident ovarian cancer with douche and genital use talc as the most important contributors to the mixture, which is consistent with the findings from both the Sister Study (Gonzalez et al., 2016) and other studies (Penninkilampi & Eslick, 2018; Wentzensen & O'Brien, 2021). Some previous studies have also demonstrated positive associations between talc use and uterine/endometrial cancer (O'Brien et al., 2019, 2021). We observed similar relationships of talc use in single-product models and the hygiene mixture use (under arm and genital talc use as the primary contributors) in multi-product models with uterine cancer incidence, although the confidence intervals were wide.

While our findings showed an inverse association between the skincare mixture and breast cancer incidence, previous studies have not found an association of individual skincare products such as skin lightener (Brinton et al., 2018), body lotion, hand cream, and facial cream (Rylander et al., 2019) with breast or endometrial cancer. Although it is possible that using skincare products may reduce risk of breast cancer, this association could also be due to residual confounding. For instance, women who frequently use skincare product may also engage in other health-seeking behaviors, which could reduce their risk of breast cancer development. However, we did not observe meaningful changes in the estimates after adjusting for additional confounders such as physical activity, smoking status, and alcohol consumption.

We observed heterogeneous associations for the beauty mixture with breast cancer and with ovarian cancer among Black and non-Hispanic White participants. Since chemical composition of products may vary based on whether they are marketed towards women of different races and ethnicities, the estimated effects for the PCP mixtures could vary. For example, women likely select different colors and levels of UV protection of cosmetic products based on their skin tone, resulting in different chemical exposures from the same type of products (Collins et al., 2021; Zota & Shamasunder, 2017). Moreover, different frequency of use within the same frequency category by Black and non-Hispanic White women could also contribute to heterogeneity. It is possible that Black women in the highest frequency category (i.e., reported using a product "more than 5 times per week") used certain products more frequently than non-Hispanic White women, or vice versa. In this study, we found that Black women used perfume, artificial nails, cuticle nail,

Table 2
Associations between one-frequency category increase in use of multiple personal care products and all, premenopausal, and postmenopausal breast, ovarian, and uterine cancer using quantile-based g-computation.

	All				Premenopausal cancer				Postmenopausal cancer				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	p_{het}[c]
Breast cancer													
Beauty	549283	43052/ 4036	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)	94550	15329/ 580	0.92 (0.78, 1.08)	0.90 (0.76, 1.07)	454721	40367/ 3419	1.08 (1.02, 1.16)	1.08 (1.01, 1.16)	0.05
Hygiene	559255	43888/ 4109	1.02 (0.94, 1.12)	1.01 (0.92, 1.10)	95357	15471/ 579	1.03 (0.80, 1.32)	1.14 (0.88, 1.48)	463887	41175/ 3493	1.03 (0.94, 1.14)	1.00 (0.91, 1.11)	0.37
Skincare	554257	43462/ 4074	0.89 (0.82, 0.97)	0.91 (0.83, 0.99)	94931	15380/ 577	0.93 (0.75, 1.15)	0.92 (0.73, 1.14)	459314	40765/ 3460	0.90 (0.81, 0.99)	0.93 (0.84, 1.02)	0.67
Ovarian cancer													
Beauty	453436	38403/ 264	1.09 (0.86, 1.37)	1.08 (0.85, 1.37)	95950	15896/ 20	0.87 (0.32, 2.41)	1.04 (0.36, 3.00)	357474	34695/ 231	1.08 (0.84, 1.39)	1.05 (0.81, 1.37)	0.95
Hygiene	461152	39092/ 267	1.49 (1.12, 1.99)	1.35 (1.00, 1.83)	96767	16038/ 21	1.77 (0.75, 4.20)	1.54 (0.61, 3.91)	364374	35360/ 233	1.49 (1.07, 2.06)	1.35 (0.97, 1.89)	0.90
Skincare	457130	38727/ 267	0.86 (0.59, 1.26)	0.84 (0.57, 1.25)	96420	15960/ 20	1.39 (0.49, 3.96)[d]	1.54 (0.52, 4.58)[d]	360786	35011/ 234	0.82 (0.53, 1.28)	0.80 (0.51, 1.27)	-[e]
Uterine cancer													
Beauty	375632	32031/ 377	1.04 (0.85, 1.27)	1.08 (0.88, 1.34)	80775	13651/ 22	0.73 (0.30, 1.82)	0.65 (0.25, 1.66)	294857	28448/ 338	1.04 (0.84, 1.29)	1.10 (0.88, 1.37)	0.28
Hygiene	381491	32559/ 390	1.27 (0.96, 1.68)	1.06 (0.79, 1.42)	81364	13758/ 23	0.99 (0.27, 3.68)	0.50 (0.11, 2.16)	300127	28942/ 351	1.31 (0.98, 1.76)	1.12 (0.83, 1.52)	0.30
Skincare	378382	32275/ 384	0.88 (0.66, 1.17)	1.09 (0.81, 1.46)	81077	13688/ 22	0.81 (0.24, 2.77)	0.91 (0.25, 3.34)	297305	28676/ 346	0.88 (0.65, 1.19)	1.10 (0.80, 1.50)	0.94

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] Accounted for age by using age as the timescale.

[b] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal); menopausal status at enrollment were excluded in premenopausal and postmenopausal models.

[c] *P*-for-heterogeneity estimated by Wald tests of outcome-by-hair-product interaction terms from joint adjusted models.

[d] Remove product age spot lightener and skin lightener due to low case counts in some frequency categories (including these products yield infinite confidence intervals).

[e] Unable to estimate *p*-for-heterogeneity due to different products included in the mixture for premenopausal and postmenopausal analyses.

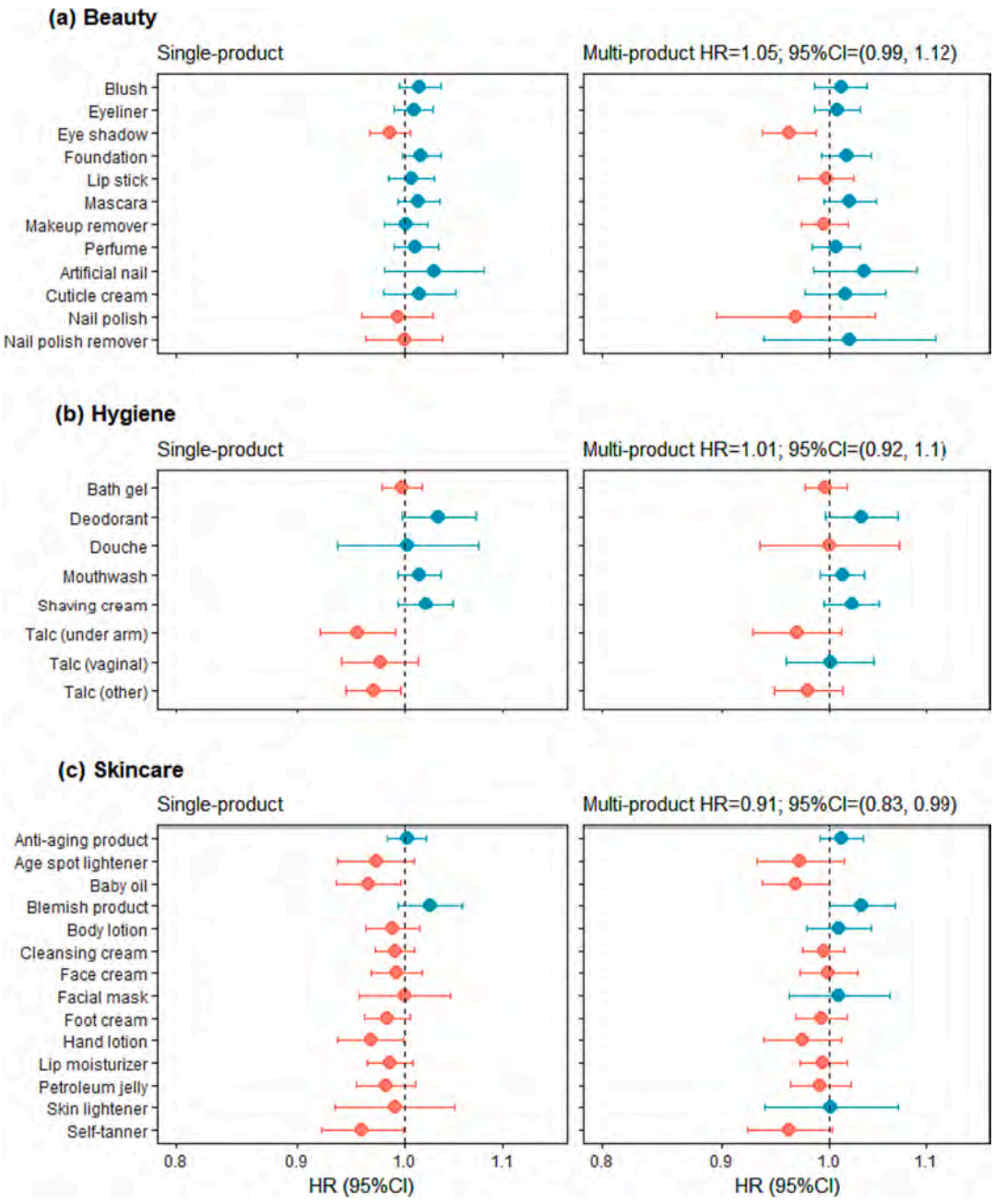

Fig. 3. Adjusted associations between one-frequency category increase in use of personal care products and breast cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

and nail polish remover more frequently than non-Hispanic White participants. Given these products are the primary positive contributors within the beauty mixture to ovarian cancer incidence, this may partly explain why the effect of the beauty mixture on ovarian cancer appears to be stronger in Black women.

Our findings provide some evidence showing that EDC exposure from PCPs may play a role in the etiology of hormone-sensitive cancers, with the positive association between the beauty mixture and breast cancer incidence only identified in postmenopausal women. Additionally, the hygiene and skincare mixtures exhibit stronger positive associations with ovarian cancer among leaner women. These observations are consistent with previous studies indicating a greater impact of exogenous hormone exposure in a relatively low hormone environment (Calle & Kaaks, 2004; Huang et al., 1997; Simpson, 2003; Tworoger et al., 2005). Specifically, environmental EDCs (Parada et al., 2019) and hormone replacement therapy (Green et al., 2012; Riman et al., 2001) have been shown to have a stronger effect on breast cancer in women with low BMI and in their postmenopausal years. However, as

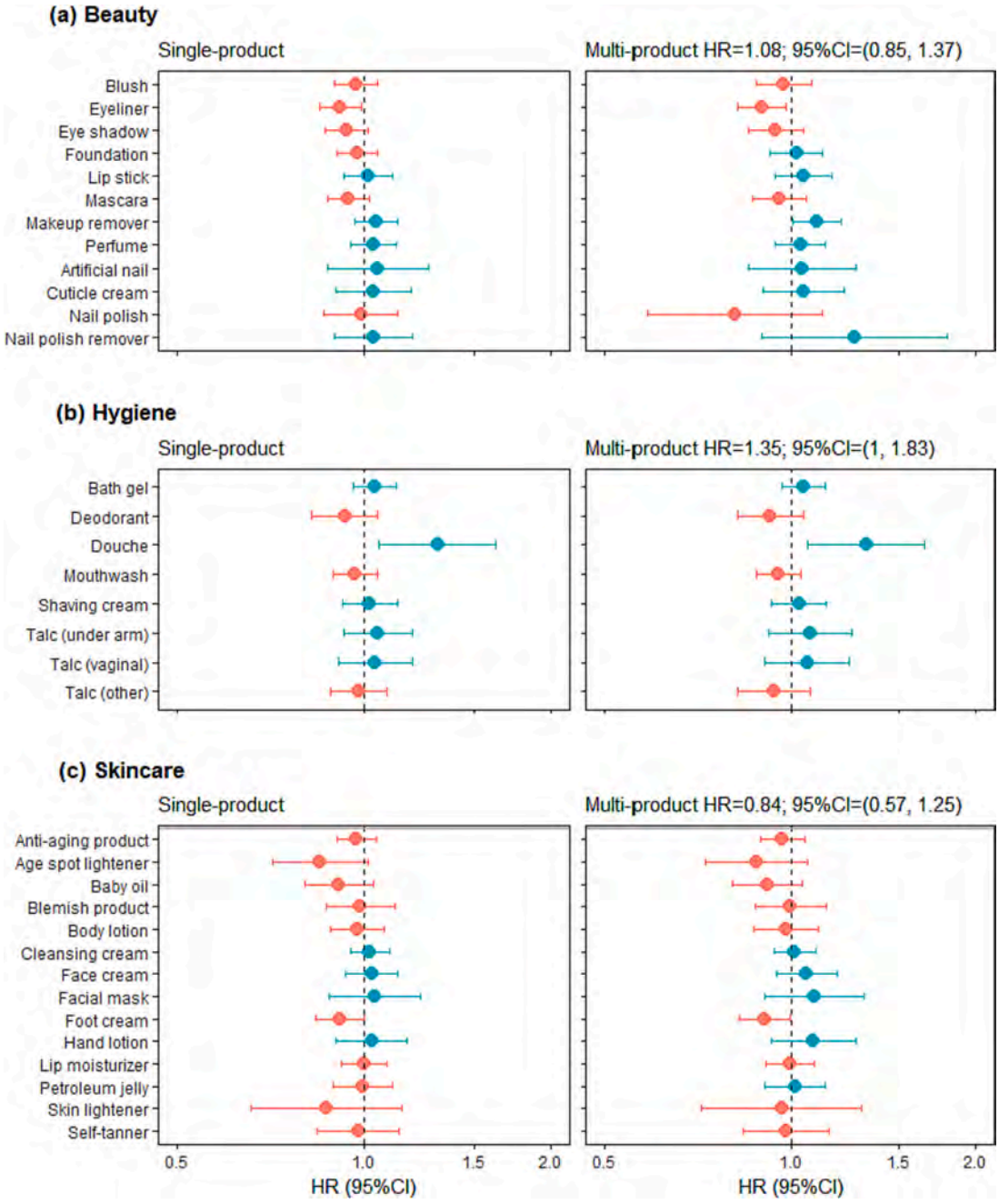

Fig. 4. Adjusted associations between one-frequency category increase in use of personal care products and ovarian cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

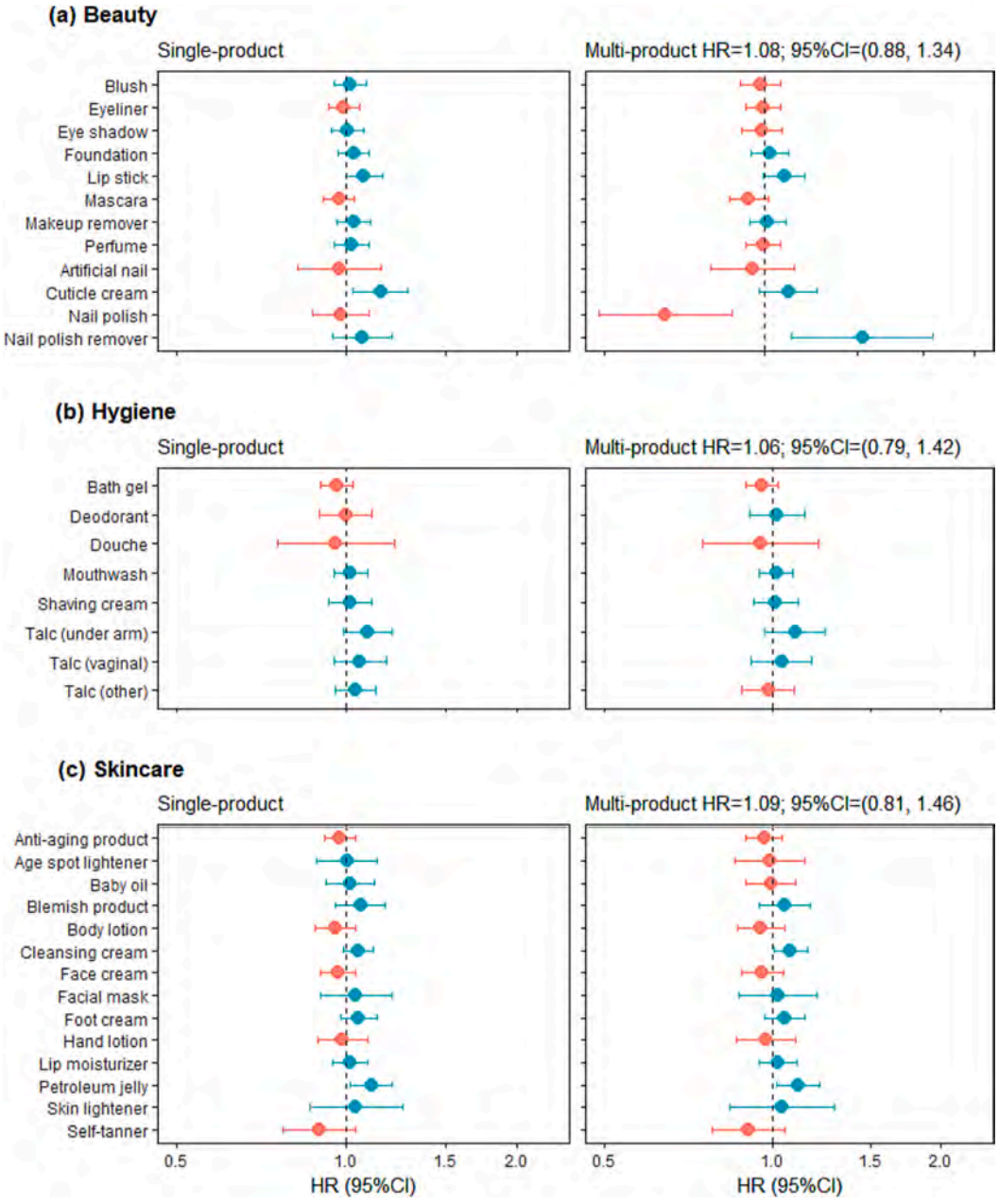

Fig. 5. Adjusted associations between one-frequency category increase in use of personal care products and uterine cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

Table 3
Associations between one-frequency category increase in use of multiple personal care products and breast, ovarian, and uterine cancer by Black and non-Hispanic White women using quantile-based g-computation.

	Black[a]				Non-Hispanic White				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[b]	Fully adjusted HR (95%CI)[b,c]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[b]	Fully adjusted HR (95%CI) [b,c]	p_{het}[d]
Breast cancer									
Beauty	42107	3632/ 312	0.84 (0.68, 1.05)	0.85 (0.68, 1.05)	471716	36398/ 3483	1.08 (1.02, 1.16)	1.08 (1.01, 1.15)	0.04
Hygiene	43328	3740/ 323	0.96 (0.71, 1.29)	0.97 (0.72, 1.30)	479593	37045/ 3544	1.03 (0.93, 1.14)	1.02 (0.92, 1.13)	0.72
Skincare	42711	3686/ 317	0.75 (0.51, 1.10)	0.75 (0.51, 1.10)	475753	36722/ 3518	0.94 (0.85, 1.04)	0.97 (0.88, 1.08)	0.21
Ovarian cancer									
Beauty	34110	3156/ 23	3.67 (1.57, 8.57)	3.62 (1.55, 8.46)	389814	32561/ 230	0.96 (0.74, 1.24)	0.95 (0.72, 1.24)	<0.01
Hygiene	35065	3249/ 22	1.10 (0.40, 3.05)	1.04 (0.37, 2.92)	395931	33099/ 233	1.42 (1.01, 2.00)	1.25 (0.88, 1.78)	0.73
Skincare	34563	3202/ 23	0.88 (0.16, 4.92)	0.91 (0.16, 5.10)	392892	32822/ 233	0.56 (0.30, 1.07)	0.57 (0.30, 1.10)	0.63
Uterine cancer									
Beauty	23914	2318/ 31	1.32 (0.62, 2.83)	1.42 (0.66, 3.05)	328002	27519/ 326	0.98 (0.79, 1.23)	1.04 (0.82, 1.31)	0.44
Hygiene	24542	2380/ 32	2.35 (0.93, 5.92)	2.19 (0.86, 5.59)	332718	27936/ 338	1.04 (0.73, 1.48)	0.92 (0.64, 1.32)	0.09
Skincare	24224	2351/ 30	1.28 (0.66, 2.47)[e]	1.46 (0.75, 2.86)[e]	330321	27716/ 335	0.67 (0.43, 1.03)	0.83 (0.53, 1.30)	-[f]

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] All African American/Black including Hispanic Black.

[b] Accounted for age by using age as the timescale.

[c] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

[d] *P*-for-heterogeneity estimated by Wald tests on augmented race-by-product terms in the adjusted models.

[e] Remove age spot lightener, skin lightener, and self-tanner due to low case counts in some frequency categories (including these products yield infinite confidence intervals).

[f] Unable to estimate *p*-for-heterogeneity due to different products included in the mixture for Black and non-Hispanic White analyses.

Table 4
Associations between one-frequency category increase in use of multiple personal care products and breast, ovarian, and uterine cancer by body mass index (BMI) groups using quantile-based g-computation.

	BMI <25				25≤ BMI <30				BMI ≥30				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI) [a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI) [a,b]	p_{het}[c]
Breast cancer													
Beauty	220673	17030/ 1463	1.03 (0.93, 1.15)	1.00 (0.93, 1.15)	172790	13535/ 1317	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)	155820	12487/ 1256	1.10 (0.99, 1.22)	1.10 (0.99, 1.22)	0.51
Hygiene	223496	17273/ 1469	1.10 (0.94, 1.28)	1.12 (0.96, 1.30)	176022	13794/ 1354	1.07 (0.92, 1.25)	1.09 (0.93, 1.27)	159737	12821/ 1286	0.82 (0.71, 0.96)	0.83 (0.72, 0.97)	0.14
Skincare	221730	17122/ 1458	0.96 (0.83, 1.11)	0.96 (0.83, 1.11)	174429	13665/ 1339	0.89 (0.76, 1.03)	0.88 (0.75, 1.03)	158098	12675/ 1277	0.87 (0.74, 1.02)	0.86 (0.73, 1.02)	0.45
Ovarian cancer													
Beauty	190528	15785/ 93	1.19 (0.82, 1.74)	1.18 (0.80, 1.72)	140758	11953/ 81	1.37 (0.93, 2.02)	1.38 (0.93, 2.04)	122150	10665/ 90	0.69 (0.42, 1.13)	0.69 (0.42, 1.14)	0.48
Hygiene	192781	15983/ 94	2.29 (1.47, 3.56)	2.14 (1.37, 3.35)	143319	12181/ 81	0.97 (0.50, 1.86)	0.91 (0.47, 1.76)	125052	10928/ 92	1.17 (0.71, 1.93)	1.12 (0.67, 1.86)	<0.01
Skincare	191227	15847/ 94	1.33 (0.76, 2.30)	1.30 (0.74, 2.26)	142063	12064/ 83	0.63 (0.26, 1.54)	0.60 (0.25, 1.47)	123840	10816/ 90	0.46 (0.19, 1.13)	0.44 (0.18, 1.08)	0.03
Uterine cancer													
Beauty	166933	13895/ 90	1.05 (0.66, 1.68)	1.13 (0.71, 1.81)	113958	9794/ 106	1.10 (0.75, 1.63)	1.18 (0.80, 1.76)	94742	8351/ 181	0.94 (0.71, 1.25)	1.00 (0.75, 1.34)	0.77
Hygiene	168774	14067/ 92	0.89 (0.42, 1.88)	0.92 (0.44, 1.94)	115890	9965/ 110	1.22 (0.73, 2.04)	1.24 (0.74, 2.07)	96826	8527/ 188	1.01 (0.68, 1.51)	1.02 (0.68, 1.54)	0.68
Skincare	167443	13945/ 94	1.39 (0.85, 2.29)	1.50 (0.91, 2.46)	114949	9882/ 107	0.77 (0.40, 1.45)	0.84 (0.44, 1.60)	95990	8430/ 183	0.79 (0.50, 1.26)	0.85 (0.53, 1.37)	0.68

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] Accounted for age by using age as the timescale.

[b] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (<25, 25-<30, ≥30), product term of BMI (<25, 25-<30, ≥30) and menopausal status at enrollment (premenopausal, postmenopausal).

[c] *P*-for-heterogeneity estimated by Wald tests on augmented BMI-by-product terms in the adjusted models.

the similar heterogeneity was not consistently observed in every product mixture or all three hormone-sensitive cancers, more studies are necessary to further elucidate the underlying biological pathways for the relationship between PCP exposures and breast, ovarian, and uterine cancer.

Our focus on product mixtures is a strength of this analysis. While a single PCP, especially the everyday products considered here, may only have a small impact on hormone-sensitive cancer development, using multiple products could collectively have greater effects. To address this, we used quantile-based g-computation to explicitly estimate the joint effects of exposure to PCP mixtures, which may be difficult to quantify using single-product approaches. Moreover, compared to the previous LCA-based grouping, where the groups labeled as "frequent users" of products can nonetheless contain a portion of infrequent users, the effect from high exposure estimated by quantile-based g-computation could be stronger and more straightforward because the effect corresponds to frequent use of all PCPs within a mixture. Additional strengths include our large sample size, prospective study design which minimizes recall bias and reverse causation, and comprehensive questionnaire data on PCP and potential confounders.

We did not collect information on product brands or ingredients, which prevented us from directly examining the impact of specific chemicals or examining trends in products over time. However, self-reported product use may better reflect the real-world exposures to complicated chemical mixtures, which might not be disclosed by manufacturers on the labels or might be derivatives or contaminants arising during production or storage. Self-reported product use may also more accurately estimate the chronic exposure to short-lived chemicals, which would be difficult to reliably assess using biomarkers (Ahern et al., 2022; Rivera-Núñez et al., 2021). We only evaluated product use in the 12 months prior to the baseline. Although douche and genital talc use have shown to be consistently reported over time (O'Brien et al., 2023), we did not have information on other PCP use over the lifetime. In addition, given the limited case counts, particularly for ovarian and uterine cancer, the analyses for some cancer subtypes or modifications yielded wide confidence intervals.

This study utilized a sophisticated mixtures approach to examine the relationships between everyday PCPs and the incidence of hormone-sensitive cancers in a large prospective cohort in the U.S. Our findings contribute to a growing body of evidence on a possible collective effect of PCP use and breast cancer using a different analytic approach and provides novel information on associations between the PCP mixtures and ovarian and uterine cancer. Although the observed effects of a one-frequency level increase were modest in magnitude, the impact would be more substantial when comparing the most frequent users with never users. For example, an 8% higher hazard of postmenopausal breast cancer for a one-frequency level increase in the beauty mixture use could translate to approximately a 36% higher hazard for the most frequent users compared with never users. Future efforts are warranted to consider PCP exposure in relation to hormone-sensitive cancers in different populations, where patterns of use and chemicals in products may differ.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data necessary to reproduce the current analysis are publicly available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

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Data Sharing

All data necessary to reproduce the current analysis are publicly available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108298.

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